EXHIBIT A

CONTROLLED-RELEASE COMPOSITIONS CONTAINING OPIOID AGONIST AND ANTAGONIST

BACKGROUND OF THE INVENTION

Opioids, also known as opioid agonists, are a group of drugs that exhibit opium or morphine-like properties. Opioid agonists are known in the literature and to those skilled in the art (Merck Manual, 16th Ed. (1992)). Because of their analgesic efficacy, opioid agonists have been used to provide pain relief to patients.

Opioid agonists, although providing the needed analgesia for pain relief, are also associated with side effects. For example, it has been reported that administration of opioid agonists such as morphine is associated with side effects, including nausea, vomiting, pruritis, urinary retention, and respiratory depression. Gan, et al. Anesthesiology, vol. 87, No. 5, 1075-1081 (1997). Chronic use of morphine has also been reported to increase physical dependence and increase tolerance of the drug, Shen et al., Brain Res., Vol. 597, 74-83 (1992), and to induce constipation.

Attempts to reduce the side effects of opioid agonists, without affecting its analgesic efficacy, have also been reported. One such example is provided Gan, et al. Anesthesiology, vol. 87, No. 5, 1075-1081 (1997). Gan reports that the administration of 0.25 ug.kg-^{1}.h-^{1} or 1 ug.kg-^{1}.h-^{1} naloxone (opioid antagonist) by infusion concomitantly with intravenous morphine, was

effective in reducing certain potential side effects of morphine (e.g., the incidence of nausea, vomiting and prurities).

Furthermore, U.S Patent Nos. 5,512,578; 5,472,943; 5,580,876; and 5,767,125, all to Crain et al. ("the Crain patents"), each of which are hereby incorporated by reference in their entireties, describe combinations of opioid antagonists with morphine or other bimodally acting opioid agonists. The combinations described therein are said to enhance the analgesic effects of the bimodal opioid agonist, while at the same time attenuating the physical dependence, tolerance, hyperexcitability, hyperalgeia, and other undesirable (excitatory) side effects associated with chronic use of bi-modally acting opioid agonists.

All of the documents cited in this application are incorporated herein by reference in their entireties.

Although the above-cited documents report combinations of an opioid agonist with antagonist, they do not contemplate providing a mechanism or manner of preparation of the combination dosage form in which the agonist and the antagonist are each released from the dosage form in a controlled-release manner, allowing the agonist and antagonist to be absorbed by the patient, such that the requisite analgesia together with reduction of opioid agonist related side effects and/or increased opioid potency may be provided throughout the dosing period.

The above-cited documents also do not provide controlled-release formulations for maintaining the analgesically effective blood-levels of agonist during an extended period of time, while at the same time maintaining the pharmacologically effective blood levels of the antagonist for reducing the side effects associated with the opioid treatment. Such controlled-release composition is desirable because it allows limitation of the occurrence of undesirable peak concentrations and increase patient compliance because the drug is taken less frequently.

OBJECT AND SUMMARY OF THE INVENTION

It is an object of the invention to promote patient compliance and thereby increase the efficacy of opioid agonist treatment in patients who are being treated with opioid agonist.

It is a further object of the invention to reduce the side effects associated with opioid agonist treatment.

It is also an object of the invention to provide agonist therapy in which the analgesically effective blood levels of the opioid agonist is maintained during an extended period of time, while also maintaining the pharmacologically effective blood levels of the antagonist for reducing the side effects associated with the opioid treatment.

In view of the above-mentioned objects and others, the invention is directed to a controlled release oral dosage form comprising opioid agonist and opioid antagonist, wherein the dosage form releases the opioid agonist and the antagonist in a controlled-release manner.

The invention is further directed to a controlled-release dosage form comprising an opioid agonist and the opioid antagonist, wherein the opioid agonist or the opioid antagonist, before it is combined with the other, is treated to modify its release rate, such that when combined into the controlled-release dosage form, the opioid agonist and the antagonist are released from the dosage form at appropriately similar times.

The invention is further directed to a controlled-release dosage form comprising opioid agonist and opioid antagonist, wherein the opioid agonist is present in an amount that is analgesically effective when administered to a human, and wherein the opioid antagonist is present in an amount which does not cause a reduction in the level of analgesia provided by the

dosage form to a non-therapeutic level. In certain embodiments, the opioid antagonist is also present in an amount that is effective in reducing opioid-related side effects.

In certain embodiments of the present invention, the controlled-release dosage form comprises a transdermal delivery system, an oral mucosal delivery system, a composition for intranasal administration, an injectable composition, and a solid oral composition. In certain preferred embodiments, the present invention comprises a solid, oral dosage form.

In certain preferred embodiments, the opioid agonist is selected from the group consisting of hydromorphone, oxycodone, hydrocodone, morphine and a pharmaceutically acceptable salt thereof.

In certain preferred embodiments, the opioid antagonist is selected from the group consisting of naltrexone, naloxone, nalmefene and a pharmaceutically acceptable salt thereof.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is directed to a controlled-release dosage form comprising an opioid agonist and an opioid antagonist, the oral dosage form providing controlled-release of the opioid agonist and controlled-release of the opioid antagonist. In preferred embodiments, the release rate of the agonist and the antagonist from the dosage form are controlled to maintain an analgesically effective amount of the agonist in the blood throughout the dosing period and maintain the concentration of the opioid agonist throughout the dosing period sufficient for decreasing the side effects associated with the opioid agonist but not sufficient to negate the analgesic efficacy of the agonist.

The present invention is further directed to a controlled-release solid oral dosage form comprising an opioid agonist and an opioid antagonist, the oral dosage form providing

controlled-release of the opioid agonist and controlled-release of the opioid antagonist, the dosage form, when administered to patients, provides analgesia together with reduction of side effects associated with opioid agonist. It is preferred that such dosage form releases the opioid agonist and the antagonist at substantially proportionate rates. Preferably, the release rates of the opioid agonist and antagonist are approximately proportionate over time, more preferably over a dosing period.

In certain embodiments, the controlled-release composition of the present invention provides reduction of opioid associated side effects, e.g., nausea, vomiting, pruritis, urinary retention, respiratory depression, constipation, physical dependence, tolerance, hyperexcitability, and hyperalgeia.

The term "controlled-release dosage form," refers to a dosage form which provides a longer period of pharmacological response after the administration of the agonist and the antagonist than is ordinarily provided after the administration of the rapid release dosage form. In certain preferred embodiments of the invention, the controlled-release dosage form releases the opioid agonist and the opioid agonist from the dosage form at such a rate that blood (e.g., plasma) concentration (levels) are maintained within the analgesically effective range (above the minimum effective analgesic concentration or "MEAC") over a dosing period. In certain embodiments of the invention, the opioid antagonist is released from the controlled-release dosage form at such a rate that blood (e.g., plasma) concentration of the antagonist are maintained within the pharmacologically effective range for reducing the opioid agonist associated side effects over a dosing period.

In preferred embodiments, the controlled-release dosage form of the present invention is a twice-a-day or a once-a-day opioid agonist/antagonist formulation.

Opioid agonist useful in the present invention include, but are not limited to, alfentanil,

allylprodine, alphaprodine, anileridine, benzylmorphine, bezitramide, buprenorphine, butorphanol, clonitazene, codeine, desomorphine, dextromoramide, dezocine, diampromide, diamorphone, dihydrocodeine, dihydromorphine, dimenoxadol, dimepheptanol, dimethylthiambutene, dioxaphetyl butyrate, dipipanone, eptazocine, ethoheptazine, ethylmethylthiambutene, ethylmorphine, etonitazene, fentanyl, heroin, hydrocodone, hydromorphone, hydroxypethidine, isomethadone, ketobemidone, levorphanol, levophenacylmorphan, lofentanil, meperidine, meptazinol, metazocine, methadone, metopon, morphine, myrophine, narceine, nicomorphine, norlevorphanol, normethadone, nalorphine, nalbuphene, normorphine, norpipanone, opium, oxycodone, oxymorphone, papaveretum, pentazocine, phenadoxone, phenomorphan, phenazocine, phenoperidine, piminodine, piritramide, propheptazine, promedol, properidine, propoxyphene, sufentanil, tilidine, tramadol, mixtures of any of the foregoing, salts of any of the foregoing, and the like.

In certain preferred embodiments, the opioid agonist is selected from the group consisting of hydrocodone, morphine, hydromorphone, oxycodone, codeine, levorphanol, meperidine, methadone, or salts thereof or mixtures thereof. In certain preferred embodiments, the opioid agonist is oxycodone or hydrocodone. Equianalgesic doses of these opioids, in comparison to a 15 mg dose of hydrocodone, are set forth in Table 1 below:

Table 1: Equianalgesic Doses of Opioids

Opioid	Calculated Dose (mg)
Oxycodone	13.5
Codeine	90.0
Hydrocodone	15.0
Hydromorphone	3.375

Levorphanol	1.8
Meperidine	135.0
Methadone	9.0
Morphine	27.0

In certain embodiments of the invention, the opioid agonist is a bimodally acting opioid agonist. "Bimodally acting opioid agonists" are opioid agonist that bind to and activate both inhibitory and excitatory opioid receptors on nociceptive neurons which mediate pain. Activation of the inhibitory receptors results in opioid analgesia, whereas the activation of the excitatory receptors results in undesirable side effects, including the development of physical dependence and tolerance to the opioid agonist, anti-analgesic actions, hyperexcitability and hyperalgeia. Examples of bimodally acting opioid agonists include morphine, codeine, fenfenyl analogs, pentazocine, methadone, buprenorphine, enkephalins, dynorphias, endorphins and similarly acting opioid alkaloids and opioid peptides.

The opioid antagonist useful for the present invention includes naltrexone, nalmefene, cyclazacine, levallorphan and mixtures thereof. In certain preferred embodiments, the opioid antagonist is naloxone or naltrexone.

For purposes of the present invention, the term "opioid agonist" is interchangeable with the term "opioid" or "opioid analgesic" and shall include the base of the opioid, mixed agonist-antagonists, partial agonists, pharmaceutically acceptable salts thereof, stereoisomers thereof, ethers and esters thereof, and mixtures thereof.

For purposes of the present invention, the term "opioid antagonist" shall include the base, pharmaceutically acceptable salts thereof, stereoisomers thereof, ethers and esters thereof, and

mixtures thereof.

The invention disclosed herein is meant to encompass all pharmaceutically acceptable salts thereof of the disclosed opioid agonists and antagonists. The pharmaceutically acceptable salts include, but are not limited to, metal salts such as sodium salt, potassium salt, secium salt and the like; alkaline earth metals such as calcium salt, magnesium salt and the like; organic amine salts such as triethylamine salt, pyridine salt, picoline salt, ethanolamine salt, triethanolamine salt, dicyclohexylamine salt, N,N'-dibenzylethylenediamine salt and the like; inorganic acid salts such as hydrochloride, hydrobromide, sulfate, phosphate and the like; organic acid salts such as formate, acetate, trifluoroacetate, maleate, tartrate and the like; sulfonates such as methanesulfonate, benzenesulfonate, p-toluenesulfonate, and the like; amino acid salts such as arginate, asparginate, glutamate and the like.

Some of the opioid agonists and antagonists disclosed herein may contain one or more asymmetric centers and may thus give rise to enantiomers, diastereomers, and other stereoisomeric forms. The present invention is also meant to encompass all such possible forms as well as their racemic and resolved forms and mixtures thereof. When the compounds described herein contain olefinic double bonds or other centers of geometric asymmetry, and unless specified otherwise, it is intended to include both E and Z geometric isomers. All tautomers are intended to be encompassed by the present invention as well

As used herein, the term "stereoisomers" is a general term for all isomers of individual molecules that differ only in the orientation of their atoms is space. It includes enantiomers and isomers of compounds with more than one chiral center that are not mirror images of one another (diastereomers).

The term "chiral center" refers to a carbon atom to which four different groups are attached.

The term "enantiomer" or "enantiomeric" refers to a molecule that is nonsuperimposeable on its mirror image and hence optically active wherein the enantiomer rotates the plane of polarized light in one direction and its mirror image rotates the plane of polarized light in the opposite direction.

The term "racemic" refers to a mixture of equal parts of enantiomers and which is optically inactive.

The term "resolution" refers to the separation or concentration or depletion of one of the two enantiomeric forms of a molecule.

The present invention is further directed to a method of decreasing the potential for abuse of an opioid agonist in an oral dosage form. The method comprises providing the opioid agonist in an oral dosage form as described herein.

The controlled-release compositions of the present invention includes, but is not limited to, a transdermal delivery system, an oral mucosal delivery system, a composition for intranasal administration, an injectable composition, and a solid oral composition.

TRANSDERMAL DELIVERY SYSTEM

The controlled release formulations of the present invention may be formulated as a transdermal delivery system, such as transdermal patches. In certain embodiments of the present invention, a transdermal patch comprises an opioid agonist and an opioid antagonist contained in a reservoir or a matrix, and an adhesive which allows the transdermal device to adhere to the skin, allowing the passage of the active agent from the transdermal device through the skin of the patient. Once the agonist/antagonist has penetrated the skin layer, the drugs are absorbed into the blood stream where they exert desired pharmaceutical effects. The transdermal patch releases

both the opioid agonist and the opioid antagonist in a controlled-release manner, such that the blood levels of the opioid agonist is maintained at an analgesically effective level through out the dosing period, and the blood levels of the antagonist is maintained at a concentration that is sufficient to reduce side effects associated with the opioid agonist but not sufficient to negate the analgesic effectiveness of the opioid.

Transdermal delivery system providing a controlled-release of an opioid agonist is known. For example, Duragesic® patch(commercially available from Janssen Pharmaceutical) contains an opioid agonist (fentanyl) and is said to provide adequate analgesia for up to 48 to 72 hours (2 to 3 days).

Transdermal delivery systems containing buprenorphine (an opioid agonist), for providing prolonged analgesia, are also described. Although other types of opioid analgesic transdermal formulations have been reported in the literature (such as fentanyl, discussed above), buprenorphine transdermal delivery systems are of particular interest because buprenorphine is a potent, partial agonist opioid analgesic with desirable therapeutic properties. For example, buprenorphine is 50 to 100 times more potent than morphine, but has a much safer therapeutic index than morphine (see Wallenstein SL, *et al.*, Crossover Trials in Clinical Analgesic Assays: Studies of Buprenorphine and Morphine, Pharmacotherapy, G(5): 225-235, 1986 hereby incorporated by reference).

There are several types of transdermal formulations of buprenorphine reported in the literature. See, for example, U.S. Patent No. 5,240,711 (Hille *et al.*), U.S. Patent No. 5,225,199 (Hidaka *et al.*), U.S. Patent No. 5,069,909 (Sharma *et al.*), U.S. Patent No. 4,806,341 (Chien *et al.*), and U.S. Patent No. 5,026,556 (Drust *et al.*), all of which are hereby incorporated by reference.

The transdermal delivery system used in the present invention may also be prepared in accordance with U.S. Patent No. 5,069,909 (Sharma *et al.*), hereby incorporated by reference. This patent describes a laminated composite for administering buprenorphine transdermally to treat pain. The transdermal delivery system used in the present invention may also be prepared in accordance with U.S. Patent No. 4,806,341 (Chien *et al.*), hereby incorporated by reference. This patent describes a transdermal morphinan narcotic analgesic or antagonist (including

buprenorphine) pharmaceutical polymer matrix dosage unit having a backing layer which is substantially impervious to the buprenorphine, and a polymer matrix disc layer which is adhered to the backing layer and which has microdispersed therein effective dosage amounts of the buprenorphine.

The transdermal delivery system used in the present invention may also be that described in U.S. Patent No. 5,026,556 (Drust *et al.*), hereby incorporated by reference. Therein, compositions for the transdermal delivery of buprenorphine comprise buprenorphine in a carrier of a polar solvent material selected from the group consisting of C_3-C_4 diols, C_3-C_6 triols, and mixtures thereof, and a polar lipid material selected from the group consisting of fatty alcohol esters, fatty acid esters, and mixtures thereof; wherein the polar solvent material and the lipid material are present in a weight ratio of solvent material:lipid material of from 60:40 to about 99:1. The transdermal delivery system used in the present invention may also be that described in U.S. Patent No. 4,588,580 (Gale, *et. al.*), hereby incorporated by reference. That system comprises a reservoir for the drug having a skin proximal, material releasing surface area in the range of about 5-100 cm^2 and containing between 0.1 and 50% by weight of a skin permeable form of the buprenorphine. The reservoir contains an aqueous gel comprising up to about 47-95% ethanol, 1-10% gelling agent, 0.1-10% buprenorphine, and release rate controlling means disposed in the flow path of the drug to the skin which limits the flux of the buprenorphine from the system through the skin.

The present invention is contemplated to encompass all such transdermal formulations as described above, with the inclusion of an opioid antagonist, such that the opioid antagonist is released in a controlled-release manner along with the opioid agonist.

ORAL MUCOSAL DELIVERY SYSTEM

In certain embodiments of the present invention, the controlled release opioid agonist/antagonist formulation may be prepared as a controlled-release oral mucosal delivery system. Such a system is described by McQuinn, R. L. *et al.*, "Sustained Oral Mucosal Delivery in Human Volunteers J. Controlled Release; (34) 1995 (243-250). Therein, oral mucosal patches were prepared by homogeneously mixing buprenorphine free base (8%), Carbopol 934 (52%), polyisobutylene (35%) and polyisoprene (5%, w/w) via a two-roll mill and then compressing the mixture to the appropriate thickness. A membrane backing (ethylcellulose) was

applied to one side of the compressed material and then circular disks (0.5 cm^2) were punched from the material. The backing was included in order to retard drug release from one side of the disk and to prohibit adhesion to opposing side tissues. Each soft, flexible disk was approximately 0.6 mm thick and contained 2.9 mg buprenorphine. These patches were worn by the subjects for 12 hours. Gum and lip application was tested, although adhesion at the gum site was considered superior. After the initial appearance of serum buprenorphine ($\geq$ 25 pg/ml), levels generally increased relatively rapidly and persisted until the patch was removed. After the patch was removed, buprenorphine levels fell promptly and were at a relatively low (but measureable) level by 24 hours post-dose. It was estimated that 0.42 $\pm$ 0.18 mg were delivered via the gum treatment. From this discussion, it is apparent that an oral mucosal patch can be prepared which will provide plasma concentrations considered desirable according to the present invention.

The present invention is contemplated to encompass all such oral mucosal delivery system as described above, with the inclusion of an opioid antagonist, such that the opioid antagonist is released in a controlled-release manner along with the opioid agonist.

SUPPOSITORIES

The controlled release formulations of the present invention may be formulated as a pharmaceutical suppository for rectal administration comprising an opioid agonist and an opioid antagonist in a controlled release matrix, and a suppository vehicle (base). Preparation of controlled release suppository formulations is described in, e.g., U.S. Patent No. 5,215,758, hereby incorporated by reference in its entirety.

Prior to absorption, the drug must be in solution. In the case of suppositories, solution must be preceded by dissolution of the base, or the melting of the base and subsequent partition of the drug from the base into the rectal fluid. The absorption of the drug into the body may be altered by the suppository base. Thus, the particular base to be used in conjunction with a particular drug must be chosen giving consideration to the physical properties of the drug. For example, lipid-soluble drugs will not partition readily into the rectal fluid, but drugs that are only slightly soluble in the lipid base will partition readily into the rectal fluid.

Among the different factors affecting the dissolution time (or release rate) of the drugs are the surface area of the drug substance presented to the dissolution solvent medium, the pH of the solution, the solubility of the substance in the specific solvent medium, and the driving forces of the saturation concentration of dissolved materials in the solvent medium. Generally, factor affecting the absorption of drugs from suppositories administered rectally include suppository vehicle, absorption site pH, drug pKa, degree of ionization, and lipid solubility.

The suppository base chosen should be compatible with the opioid agonist/antagonist to be incorporated into the composition. Further, the suppository base is preferably non-toxic and nonirritating to mucous membranes, melts or dissolves in rectal fluids, and is stable during storage.

In certain preferred embodiments of the present invention for both water-soluble and water-insoluble drugs, the suppository base comprises a fatty acid wax selected from the group consisting of mono-, di- and triglycerides of saturated, natural . fatty acids of the chain length C12 to C18.

In preparing the suppositories of the present invention other excipients may be used. For example, a wax may be used to form the proper shape for administration via the rectal route. This system can also be used without wax, but with the addition of diluent filled in a gelatin capsule for both rectal and oral administration.

Examples of suitable commercially available mono-, di- and triglycerides include saturated natural fatty acids of the 12-18 carbon atom chain sold under the trade name Novata TM (types AB, AB, B,BC, BD, BBC, E, BCF, C, D and 299), manufactured by Henkel, and Witepsol TM (types H5, H12, H15, H175, H185, H19, H32, H35, H39, H42, W25, W31, W35, W45, S55, S58, E75, E76 and E85), manufactured by Dynamit Nobel.

Other pharmaceutically acceptable suppository bases may be substituted in whole or in part for the above-mentioned mono-, di- and triglycerides. The amount of base in the suppository is determined by the size (i.e. actual weight) of the dosage form, the amount of alginate and drug used. Generally, the amount of suppository base is from about 20 percent to about 90 percent by weight of the total weight of the suppository. Preferably, the amount of base in the suppository is

from about 65 percent to about 80 percent, by weight of the total weight of the suppository.

In certain embodiments, the controlled-release matrix comprises a pharmaceutically acceptable sodium alginate and a pharmaceutically acceptable calcium salt, the calcium salt being in an amount sufficient to cross-link with the sodium alginate and thereby provide controlled-release of the opioid agonist and the antagonist from the matrix when the suppository base melts subsequent to administration.

COMPOSITIONS FOR INTRANASAL ADMINISTRATION

The controlled release formulation of the present invention includes compositions for nasal administration. Controlled release dosage forms containing an opioid agonist is described in European Patent No. EP 205282 and PCT Application No. WO 8203768 (both providing controlled release of morphine), and also in U.S. Patent No. 5,629,011 (morphine-6-glucuronide and morphine-6-sulfate, both being metabolites of morphine). Each of these documents are incorporated herein by reference in their entireties. The present invention is contemplated to encompass all such nasal formulations as described above, with the inclusion of an opioid antagonist, such that the opioid antagonist is released in a controlled-release manner.

In certain embodiments, the nasal composition comprises an opioid agonist and the opioid antagonist in bioadhesive microspheres. Preferably the microspheres are prepared from a bio-compatible material that will gel in contact with the mucosal surface. Substantially uniform solid microspheres are preferred. Starch microspheres (crosslinked if necessary) are a preferred material. Other materials that can be used to form microspheres include starch derivatives, modified starches such as amylodextrin, gelatin, albumin, collagen, dextran and dextran derivatives, polyvinyl alcohol, polylactide-co-glycolide, hyaluronic acid and derivatives thereof such as benzyl and ethyl esters, gellan gum and derivatives thereof such as benzyl and ethyl esters and pectin and derivatives thereof such as benzyl and ethyl esters. By the term "derivatives" we particularly mean esters and ethers of the parent compound that can be unfunctionalised or functionalised to contain, for example, ionic groupings.

Suitable starch derivatives include hydroxyethyl starch, hydroxypropyl starch,

carboxymethyl starch, cationic starch, acetylated starch, phosphorylated starch, succinate derivatives of starch and grafted starches. Such starch derivatives are well known and described in the art (for example Modified Starches: Properties and Uses, O. B. Wurzburg, CRC Press Boca Raton (1986)).

Suitable dextran derivatives include, diethylaminoethyl-dextran (DEAE-dextran) , dextran sulphate, dextran methyl-benzylamide sulphonates, dextran methyl-benzylamide carboxylates, carboxymethyl dextran, diphosphonate dextran, dextran hydrazide, palmitoyldextran and dextran phosphate.

Preparation of these microspheres is well described in the pharmaceutical literature (see for example Davis et al., (Eds), "Microspheres and Drug Therapy", Elsevier Biomedical Press, 1984, which is incorporated herein by reference). Emulsion and phase separation methods are both suitable. For example, albumin microspheres may be made using the water-in-oil emulsification method where a dispersion of albumin is produced in a suitable oil by homogenization techniques or stirring techniques, with the addition if necessary of small amounts of an appropriate surface active agent. The size of the microspheres is largely dictated by the speed of stirring or homogenization conditions. The agitation can be provided by a simple laboratory stirrer or by more sophisticated devices such as a microfluidizer or homogenizer. Emulsification techniques are also used to produce starch microspheres as described in GB 1 518 121 and EP 223 303 as well as for the preparation of microspheres of gelatin. Proteinaceous microspheres may also be prepared by coacervation methods such as simple or complex coacervation or by phase separation techniques using an appropriate solvent or electrolyte solution. Full details of the methods of preparing these systems can be obtained from standard text books (see for example Florence and Attwood, Physicochemical Principles of Pharmacy 2nd Ed., MacMillan Press, 1988, Chapter 8).

The controlled-release nasal composition according to the invention can be administered by any appropriate method according to their form. A composition comprising microspheres or a powder can be administered using a nasal insufflator device. Example of these are already employed for commercial powder systems intended for nasal application (e.g. Fisons Lomudal System).

The insufflator produces a finely divided cloud of the dry powder or microspheres. The insufflator is preferably provided with means to ensure administration of a substantially fixed amount of the composition. The powder or microspheres may be used directly with an insufflator which is provided with a bottle or container for the powder or microspheres. Alternatively the powder or microspheres may be filled into a capsule such as a gelatin capsule, or other single dose device adapted for nasal administration. The insufflator preferably has means to break open the capsule or other device.

A composition comprising a solution or dispersion in an aqueous medium can be administered as a spray using an appropriate device such as a metered dose aerosol valve or a metered dose pump. A gas or liquid propellant can be used. Details of other devices can be found in the pharmaceutical literature (see for example Bell, A. Intranasal Delivery Devices, in Drug Delivery Devices Fundamentals and Applications, Tyle P. (ed), Dekker, New York, 1988), Remington's Pharmaceutical Sciences, Mack Publishing Co., 1975.

INJECTABLE FORMULATIONS

The controlled-release injectable compositions containing an opioid antagonist is described in, e.g., U.S. Patent No. 5,942,241 to Chasin et al, which is incorporated herein by reference in its entirety. The present invention is contemplated to encompass all such injectable formulations, with the inclusion of an opioid antagonist, such that the opioid antagonist is also released in a controlled-release manner along with the opioid agonist.

In certain embodiments, the controlled-release injectable composition comprise an opioid agonist and antagonist in controlled-release microparticles, e.g., microspheres or microcapsules. The slow release of the drugs is brought about through controlled diffusion out of the matrix and/or selective breakdown of the coating of the preparation or selective breakdown of a polymer matrix.

In certain embodiments, the slow release formulation is prepared as microspheres in a size distribution range suitable for local infiltration or injection. The diameter and shape of the microspheres or other particles can be manipulated to modify the release characteristics. For example, larger diameter microspheres will typically provide slower rates of release and reduced

tissue penetration and smaller diameters of microspheres will produce the opposite effects, relative to microspheres of different mean diameter but of the same composition. In addition, other particle shapes, such as, for example, cylindrical shapes, can also modify release rates by virtue of the increased ratio of surface area to mass inherent to such alternative geometrical shapes, relative to a spherical shape. The diameter of injectable microspheres are in a size range from, for example, from about 5 microns to about 200 microns in diameter. In a more preferred embodiment, the microspheres range in diameter from about 20 to about 120 microns.

A wide variety of biodegradable materials may be utilized to provide the controlled release injectable dosage forms. Any pharmaceutically acceptable biodegradable polymers known to those skilled in the art may be utilized. It is preferred that the biodegradable controlled release material degrade in vivo over a period of less than about two years, with at least 50% of the controlled release material degrading within about one year, and more preferably six months or less. More preferably, the controlled release material will degrade significantly within one to three months, with at least 50% of the material degrading into non-toxic residues which are removed by the body, and 100% of the drug being released within a time period from about two weeks to about two months. The controlled release material should preferably degrade by hydrolysis, and most preferably by surface erosion, rather than by bulk erosion, so that release is not only sustained but also provides desirable release rates. However, the pharmacokinetic release profile of these formulations may be first order, zero order, bi- or multi-phasic, to provide the desired reversible local anesthetic effect over the desired time period.

The controlled release material should be biocompatible. In the case of polymeric materials, biocompatibility is enhanced by recrystallization of either the monomers forming the polymer and/or the polymer Using standard techniques.

Suitable biodegradable polymers can be utilized as the controlled release material. The polymeric material may comprise a polylactide, a polyglycolide, a poly(lactide-co-glycolide), a polyanhydride, a polyorthoester, polycaprolactones, polyphosphazenes, polysaccharides, proteinaceous polymers, soluble derivatives of polysaccharides, soluble derivatives of proteinaceous polymers, polypeptides, polyesters, and polyorthoesters or mixtures or blends of any of these. The polysaccharides may be poly-1,4-glucans, e.g., starch glycogen, amylose, amylopectin, and mixtures thereof. The biodegradable hydrophilic or hydrophobic polymer may

be a water-soluble derivative of a poly-1,4-glucan, including hydrolyzed amylopectin, hydroxyalkyl derivatives of hydrolyzed amylopectin such as hydroxyethyl starch (HES), hydroxyethyl amylose, dialdehyde starch, and the like. Preferred controlled release materials which are useful in the formulations of the invention include the polyanhydrides, co-polymers of lactic acid and glycolic acid wherein the weight ratio of lactic acid to glycolic acid is no more than 4:1 (i.e., 80% or less lactic acid to 20% or more glycolic acid by weight), and polyorthoesters containing a catalyst or degradation enhancing compound, for example, containing at least 1% by weight anhydride catalyst such as maleic anhydride. Other useful polymers include protein polymers such as gelatin and fibrin and polysaccharides such as hyaluronic acid. Since polylactic acid takes at least one year to degrade in vivo, this polymer should be utilized by itself only in circumstances where such a degradation rate is desirable or acceptable.

The polymeric material may be prepared by any method known to those skilled in the art. For example, where the polymeric material is comprised of a copolymer of lactic and glycolic acid, this copolymer may be prepared by the procedure set forth in U.S. Pat. No. 4,293,539 (Ludwig, et al.), the disclosure of which is hereby incorporated by reference in its entirety. In brief, Ludwig prepares such copolymers by condensation of lactic acid and glycolic acid in the presence of a readily removable polymerization catalyst (e.g., a strong acid ion-exchange resin such as Dowex HCR-W2-H). The amount of catalyst is not critical to the polymerization, but typically is from about 0.01 to about 20 parts by weight relative to the total weight of combined lactic acid and glycolic acid. The polymerization reaction may be conducted without solvents at a temperature from about 100 C. to about 250 C. for about 48 to about 96 hours, preferably under a reduced pressure to facilitate removal of water and by-products. The copolymer is then recovered by filtering the molten reaction mixture to remove substantially all of the catalyst, or by cooling and then dissolving the reaction mixture in an organic solvent such as dichloromethane or acetone and then filtering to remove the catalyst.

The substrates of the presently described formulations in certain preferred embodiments are manufactured using a method that evenly disperses the local anesthetic throughout the formulation, such as emulsion preparation, solvent casting, spray drying or hot melt, rather than a method such as compression molding. A desired release profile may be achieved by using a mixture of polymers having different release rates.

Methods for manufacture of microspheres are well known and are typified in the following examples. Examples of suitable methods of making microspheres include solvent evaporation, phase separation and fluidized bed coating.

In solvent evaporation procedures, the local anesthetic agent, if soluble in organic solvents, may be entrapped in the biodegradable polymer by dissolving the polymer in a volatile organic solvent, adding the drug to the organic phase, emulsifying the organic phase in water which contains less than 2% polyvinyl alcohol, and finally removing the solvent under vacuum to form discrete, hardened monolithic microspheres.

Phase separation microencapsulation procedures are suitable for entrapping water-soluble agents in the polymer to prepare microcapsules and microspheres. Phase separation involves coacervation of the polymer from an organic solvent by addition of a nonsolvent such as silicone oil. In a preferred embodiment, the microspheres may be prepared by the process of Ramstack et al., 1995, in published international patent application WO 95/13799, the disclosure of which is incorporated herein in its entirety. The Ramstack et al. process essentially provides for a first phase, including an active agent and a polymer, and a second phase, that are pumped through a static mixer into a quench liquid to form microparticles containing the active agent. The first and second phases can optionally be substantially immiscible and the second phase is preferably free from solvents for the polymer and the active agent and includes an aqueous solution of an emulsifier.

In fluidized bed coating, the drug is dissolved in an organic solvent along with the polymer. The solution is then processed, e.g., through a Wurster air suspension coating apparatus to form the final microcapsule product.

PREPARATION OF CONTROLLED RELEASE ORAL DOSAGE FORMS

The opioid agonist and antagonist combination may be formulated as a controlled-release oral dosage form, including tablets and capsules. In preferred embodiments, the controlled-

release oral dosage form provides a controlled release of an opioid agonist and a controlled-release of an opioid antagonist, such that when the dosage form is administered to a human, the blood levels of the agonist is maintained throughout the dosing period at an analgesically effective level, and the antagonist at a level sufficient to decrease the side effects associated with the opioid agonist but not sufficient to negate the analgesic effect of the opioid agonist.

The term "release rate," as used in the application, refers to a rate at which a drug is released from the dosage form. The release pattern of a drug is a function of its properties, such as its physicochemical properties. Solubility is one such property. Since drug must be in solution before they can be absorbed into the body. The release rate of the drug from an oral dosage form may be measured, for example, by measuring the dissolution rate of the drug from the dosage form using an in vitro test method conducted under standardized conditions, e.g., U.S.P. paddle, 100 rpm in simulated gastric fluid for the first hour and thereafter in simulated intestinal fluid.

In certain embodiments of the present invention, the ratio of the opioid agonist and antagonist in the controlled-release oral dosage form is about 1:1 to about 100:1 by weight. In preferred embodiments, the ratio of the opioid agonist with the antagonist is about 40:1 to about 50:1 by weight, more preferably about 20:1.

The oral dosage form of the present invention may further include, in addition to an opioid agonist and antagonist, one or more drugs that may or may not act synergistically therewith. Thus, in certain embodiments, a combination of two opioid agonists may be included in the dosage form, in addition to the opioid antagonist. For example, the dosage form may include two opioid agonist having different properties, such as half-life, solubility, potency, and a combination of any of the foregoing. In yet further embodiments, one or more opioid agonist is included and a further non-opioid drug is also included, in addition to the opioid antagonist. Such non-opioid drugs would preferably provide additional analgesia, and include, for example,

aspirin, acetaminophen; non-steroidal anti-inflammatory drugs ("NSAIDS"), e.g., ibuprofen, ketoprofen, etc.; N-methyl-D-aspartate (NMDA) receptor antagonists, e.g., a morphinan such as dextromethorphan or dextrorphan, or ketamine; cycooxygenase-II inhibitors ("COX-II inhibitors"); and/or glycine receptor antagonists.

In certain preferred embodiments of the present invention, the invention allows for the use of lower doses of the opioid analgesic by virtue of the inclusion of an additional non-opioid agonist, such as an NSAID or a COX-2 inhibitor. By using lower amounts of either or both drugs, the side effects associated with effective pain management in humans are reduced.

Suitable non-steroidal anti-inflammatory agents, including ibuprofen, diclofenac, naproxen, benoxaprofen, flurbiprofen, fenoprofen, flubufen, ketoprofen, indoprofen, piroprofen, carprofen, oxaprozin, pramoprofen, muroprofen, trioxaprofen, suprofen, aminoprofen, tiaprofenic acid, fluprofen, bucloxic acid, indomethacin, sulindac, tolmetin, zomepirac, tiopinac, zidometacin, acemetacin, fentiazac, clidanac, oxpinac, mefenamic acid, meclofenamic acid, flufenamic acid, niflumic acid, tolfenamic acid, diflurisal, flufenisal, piroxicam, sudoxicam or isoxicam, and the like. Useful dosages of these drugs are well known to those skilled in the art.

N-methyl-D-aspartate (NMDA) receptor antagonists are well known in the art, and encompass, for example, morphinans such as dextromethorphan or dextrorphan, ketamine, d-methadone or pharmaceutically acceptable salts thereof. For purposes of the present invention, the term "NMDA antagonist" is also deemed to encompass drugs that block a major intracellular consequence of NMDA-receptor activation, e.g. a ganglioside such as GM_1 or GT_{1b} a phenothiazine such as trifluoperazine or a naphthalenesulfonamide such as N-(6-aminothexyl)-5-chloro-1-naphthalenesulfonamide. These drugs are stated to inhibit the development of tolerance to and/or dependence on addictive drugs, e.g., narcotic analgesics such as morphine, codeine, etc. in U.S. Pat. Nos. 5,321,012 and 5,556,838 (both to Mayer, et al.), and to treat chronic pain in U.S. Pat. No. 5,502,058 (Mayer, et al.), all of which are hereby incorporated by reference. The

NMDA antagonist may be included alone, or in combination with a local anesthetic such as lidocaine, as described in these Mayer, et.al. patents.

The treatment of chronic pain via the use of glycine receptor antagonists and the identification of such drugs is described in U.S. Pat. No. 5,514,680 (Weber, et al.), hereby incorporated by reference.

COX-2 inhibitors have been reported in the art and many chemical structures are known to produce inhibition of cyclooxygenase-2. COX-2 inhibitors are described, for example, in U.S. Patent Nos. 5,616,601; 5,604,260; 5,593,994; 5,550,142; 5,536,752; 5,521,213; 5,475,995; 5,639,780; 5,604,253; 5,552,422; 5,510,368; 5,436,265; 5,409,944; and 5,130,311, all of which are hereby incorporated by reference. Certain preferred COX-2 inhibitors include celecoxib (SC-58635), DUP-697, flosulide (CGP-28238), meloxicam, 6-methoxy-2 naphthylacetic acid (6-MNA), MK-966 (also known as Vioxx), nabumetone (prodrug for 6-MNA), nimesulide, NS-398, SC-5766, SC-58215, T-614; or combinations thereof. Dosage levels of COX-2 inhibitor on the order of from about 0.005 mg to about 140 mg per kilogram of body weight per day are therapeutically effective in combination with an opioid analgesic. Alternatively, about 0.25 mg to about 7 g per patient per day of a COX-2 inhibitor is administered in combination with an opioid analgesic.

In yet further embodiments, a non-opioid drug can be included which provides a desired effect other than analgesia, e.g., antitussive, expectorant, decongestant, antihistamine drugs, local anesthetics, and the like.

In certain preferred embodiments of the invention, the controlled release oral dosage form comprises an opioid agonist and an opioid antagonist in combination with acetominophen.

Acetaminophen is an analgesic/antipyretic drug which has been utilized for treating mild

to moderate pain such as headache, neuralgia, and musculoskeletal pain. The recommended daily adult dose is about 325 to about 650 mg every 4 hours, not to exceed a total dose of 4 g in 24 hours. The maximum dose of immediate release acetaminophen is generally considered to be about 1000 mg.

It is contemplated that the combination formulations and methods of the present invention may include such acetaminophen doses as those set forth above, or lower doses per 4 hour dosing interval. Thus, it is possible that controlled release formulations prepared in accordance with the present invention include a greater total acetominophen dose than the 325 - 650 mg dose, but that dose will be released in a controlled-release manner over a longer dosing interval (e.g., over 8 hours or more).

It is contemplated that the dosage of acetaminophen and opioid agonist in the formulations and method of the present invention may be similar or the same as dosages which are already commercially available and accepted by clinicians. Acetaminophen is commercially available in the United States in fixed combination with opioid agonists , namely, codeine, oxycodone and hydrocodone. Typical oral capsule dosages of acetaminophen/codeine combinations include 325 mg acetaminophen and 15 mg codeine phosphate, 325 mg acetaminophen and 30 mg codeine phosphate and 325 mg acetaminophen and 60 mg codeine phosphate. Tablets typically include 300 mg acetaminophen and 7.5 mg codeine phosphate, 300 mg acetaminophen and 15 mg codeine phosphate, 300 mg acetaminophen and 30 mg codeine phosphate, and 300 mg acetaminophen and 60 mg codeine phosphate.

Hydrocodone/acetaminophen capsules are typically available in fixed combinations of 5 mg hydrocodone (as the bitartrate salt) and 500 mg acetaminophen.
Hydrocodone/acetaminophen tablets are typically available in fixed combinations of 500 mg acetaminophen and 2.5 mg hydrocodone bitartrate, 500 mg acetaminophen and 5 mg hydrocodone bitartrate, 500 mg acetaminophen and 7.5 mg hydrocodone, 7.5 mg hydrocodone

bitartrate and 650 or 750 mg acetaminophen, and 10 mg hydrocodone bitartrate and 500, 650, 660 mg acetaminophen. Oxycodone/acetaminophen capsules and caplets are available in fixed combination of 5 mg oxycodone (as the hydrochloride salt) and 500 mg acetaminophen, and in tablets as 5 mg oxycodone hydrochloride and 325 mg acetaminophen.

The fixed combinations described above are for information purposes only and are not meant to limit the possible relative amounts of opioid and acetaminophen contained in the formulations encompassed within the present invention. As disclosed herein and in accordance with the present invention, it is contemplated that in certain embodiments, the opioid agonist/opioid antagonist/acetaminophen combinations encompassed herein will have greater or lesser dosages of either the opioid agonist or acetaminophen, and that the ratio of opioid agonist to acetaminophen will vary based on the particular opioid agonist and opioid antagonist chosen for a formulation and the amount of opioid antagonist included therein, among other things.

In certain preferred embodiments, the oral dosage form comprises an opioid agonist (hydrocodone or oxycodone) and opioid antagonist (naltrexone, naloxone and nalmefene) and acetaminophen.

Controlled-release oral dosage forms according the invention may be prepared using the methods available to one skilled in the art. In certain embodiments of the present invention, controlled-release tablets comprise the opioid agonist and antagonist in a controlled release matrix. The controlled-release matrix may include hydrophilic and/or hydrophobic materials, such as gums, cellulose ethers, acrylic resins, protein derived materials; the list is not meant to be exclusive, and any pharmaceutically
acceptable hydrophobic material or hydrophilic material which is capable of imparting controlled release of the opioid may be used in accordance with the present invention.

Digestible, long chain (C_8-C_{50}, especially C_{12}-C_{40}), substituted or unsubstituted

hydrocarbons, such as fatty acids, fatty alcohols, glyceryl esters of fatty acids, mineral and vegetable oils and waxes, and stearyl alcohol; and polyalkylene glycols.

Of these polymers, acrylic polymers, especially Eudragit® RSPO - the cellulose ethers, especially hydroxyalkylcelluloses and carboxyalkylcelluloses, are preferred. The oral dosage form may contain between 1% and 80% (by weight) of at least one hydrophilic or hydrophobic material. Another suitable polymer comprises a mixture of two acrylic resin lacquers commercially available from Rohm Pharma under the Tradenames Eudragit® RL30D and Eudragit® RS30D, respectively. Eudragit® RL30D and Eudragit® RS30D are copolymers of acrylic and methacrylic esters with a low content of quaternary ammonium groups, the molar ratio of ammonium groups to the remaining neutral (meth)acrylic esters being 1:20 in Eudragit® RL30D and 1:40 in Eudragit® RS30D. The mean molecular weight is about 150,000. The code designations RL (high permeability) and RS (low permeability) refer to the permeability properties of these agents.

When the hydrophobic material is a hydrocarbon, the hydrocarbon preferably has a melting point of between 25° and 90°C. Of the long chain hydrocarbon materials, fatty (aliphatic) alcohols are preferred. The oral dosage form may contain up to about 60% (by weight) of at least one digestible, long chain hydrocarbon.

Preferably, the oral dosage form contains up to about 60% (by weight) of at least one polyalkylene glycol.

The hydrophobic material is preferably selected from the group consisting of alkylcelluloses, acrylic and methacrylic acid polymers and copolymers, shellac, zein, hydrogenated castor oil, hydrogenated vegetable oil, or mixtures thereof. In certain preferred embodiments of the present invention, the hydrophobic material is a pharmaceutically acceptable acrylic polymer, including but not limited to acrylic acid and methacrylic acid copolymers,

methyl methacrylate, methyl methacrylate copolymers, ethoxyethyl methacrylates, cyanoethyl methacrylate, aminoalkyl methacrylate copolymer, poly(acrylic acid), poly(methacrylic acid), methacrylic acid alkylamine copolymer, poly(methyl methacrylate), poly(methacrylic acid)(anhydride), polymethacrylate, polyacrylamide, poly(methacrylic acid anhydride), and glycidyl methacrylate copolymers. In other embodiments, the hydrophobic material is selected from materials such as hydroxyalkylcelluloses such as hydroxypropylmethylcellulose and mixtures of the foregoing.

Preferred hydrophobic materials are water-insoluble with more or less pronounced hydrophilic and/or hydrophobic trends. Preferably, the hydrophobic materials useful in the invention have a melting point from about 30° to about 200°C, preferably from about 45° to about 90°C. Specifically, the hydrophobic material may comprise natural or synthetic waxes , fatty alcohols (such as lauryl, myristyl, stearyl, cetyl or preferably cetostearyl alcohol), fatty acids, including but not limited to fatty acid esters, fatty acid glycerides (mono-, di-, and tri-glycerides), hydrogenated fats, hydrocarbons, normal waxes, stearic aid, stearyl alcohol and hydrophobic and hydrophilic materials having hydrocarbon backbones. Suitable waxes include, for example, beeswax, glycowax, castor wax and carnauba wax. For purposes of the present invention, a wax-like substance is defined as any material which is normally solid at room temperature and has a melting point of from about 30° to about 100°C.

Suitable hydrophobic materials which may be used in accordance with the present invention include digestible, long chain (C_8-C_{50}, especially C_{12}-C_{40}), substituted or unsubstituted hydrocarbons, such as fatty acids, fatty alcohols, glyceryl esters of fatty acids, mineral and vegetable oils and natural and synthetic waxes. Hydrocarbons having a melting point of between 25° and 90°C are preferred. Of the long chain hydrocarbon materials, fatty (aliphatic) alcohols are preferred in certain embodiments. The oral dosage form may contain up to 60% (by weight) of at least one digestible, long chain hydrocarbon.

Preferably, a combination of two or more hydrophobic materials is included in the matrix formulations. If an additional hydrophobic material is included, it is preferably selected from natural and synthetic waxes, fatty acids, fatty alcohols, and mixtures of the same. Examples include beeswax, carnauba wax, stearic acid and stearyl alcohol. This list is not meant to be exclusive.

One particular suitable matrix comprises at least one water soluble hydroxyalkyl cellulose, at least one C_{12}-C_{36}, preferably C_{14}-C_{22}, aliphatic alcohol and, optionally, at least one polyalkylene glycol. The at least one hydroxyalkyl cellulose is preferably a hydroxy (C_1 to C_6) alkyl cellulose, such as hydroxypropylcellulose, hydroxypropylmethylcellulose and, especially, hydroxyethylcellulose. The amount of the at least one hydroxyalkyl cellulose in the present oral dosage form will be determined, inter alia, by the precise rate of opioid release required. The at least one aliphatic alcohol may be, for example, lauryl alcohol, myristyl alcohol or stearyl alcohol. In particularly preferred embodiments of the present oral dosage form, however, the at least one aliphatic alcohol is cetyl alcohol or cetostearyl alcohol. The amount of the at least one aliphatic alcohol in the present oral dosage form will be determined, as above, by the precise rate of opioid release required. It will also depend on whether at least one polyalkylene glycol is present in or absent from the oral dosage form. In the absence of at least one polyalkylene glycol, the oral dosage form preferably contains between 20% and 50% (by wt) of the at least one aliphatic alcohol. When at least one polyalkylene glycol is present in the oral dosage form, then the combined weight of the at least one aliphatic alcohol and the at least one polyalkylene glycol preferably constitutes between 20% and 50% (by wt) of the total dosage.

In one embodiment, the ratio of, e.g., the at least one hydroxyalkyl cellulose or acrylic resin to the at least one aliphatic alcohol/ polyalkylene glycol determines, to a considerable extent, the release rate of the opioid from the formulation. A ratio of the at least one hydroxyalkyl cellulose to the at least one aliphatic alcohol/polyalkylene glycol of between 1:2 and 1:4 is preferred, with a ratio of between 1:3 and 1:4 being particularly preferred.

The at least one polyalkylene glycol may be, for example, polypropylene glycol or, which is preferred, polyethylene glycol. The number average molecular weight of the at least one polyalkylene glycol is preferred between 1,000 and 15,000 especially between 1,500 and 12,000.

Another suitable controlled release matrix would comprise an alkylcellulose (especially ethyl cellulose), a C_{12} to C_{36} aliphatic alcohol and, optionally, a polyalkylene glycol.

In another preferred embodiment, the matrix includes a pharmaceutically acceptable combination of at least two hydrophobic materials. In addition to the above ingredients, a controlled release matrix may also contain suitable quantities of other materials, e.g. diluents, lubricants, binders, granulating aids, colorants, flavorants and glidants that are conventional in the pharmaceutical art.

In certain embodiments of the invention, the opioid antagonist and the opioid agonist are combined with suitable matrix forming material, as listed above, to prepare granulatès containing both drugs. The granulates comprise the agonist and the antagonist dispersed in a controlled-release matrix. For example, oxycodone HCl, morphine sulfate, hydromorphone HCl or hydrocodone bitartrate may be combined with naltrexone or naloxone, and granulated using suitable controlled-release matrix forming materials, e.g., Eudragit RS 30D or hydroxyethylcellulose, to produce granulates in which the opioid agonist and the antagonist are dispersed in the sustained release matrix. The granulates may be treated with wax in a melt-granulation technique in which a wax , e.g., stearyl alcohol or cetostearyl alcohol, is melted and incorporated with the drug containing granulates. Examples of controlled-release formulations prepared using melt-granulation techniques are found in U.S. Patent No. 4,861,598, which is hereby incorporated by reference in its entirety. In certain embodiments, the controlled-release carrier comprises about 10% to about 90% by weight of the dosage form, preferably about 30% to about 60%.

In certain embodiments of the invention, the opioid agonist or antagonist may be treated to modify its release rate before the drug is combined with the other to form controlled-release dosage forms. For example, it may be desirable to decrease the release rate of the antagonist before it is combined with the agonist, such that the combination dosage form releases the two drugs at substantially proportionate rates. One may slow down the release rate of the antagonist by preparing granulates comprising the antagonist dispersed in a controlled-release matrix. The opioid antagonist granulates may then be combined with opioid agonist and a suitable controlled-release matrix material to produce a controlled matrix in which the already rate-modified antagonist and the agonist are dispersed. The modification of the antagonist, before combining it with the agonist, slows down the release rate of the agonist, such that when the two drugs are combined and formulated into controlled-release dosage forms, they are released at substantially proportionate rates.

Alternatively, the opioid antagonist containing granulates may be combined with opioid containing granulates, which are separately prepared. The opioid agonist granulates comprises the agonist dispersed in a controlled-release matrix. The controlled release matrix of the opioid agonist granulates provide different releasing properties than the matrix of the antagonist, such that when the two granulates are combined and compressed into tablets, the tablets provide release profile of the two drugs that are substantially similar.

In certain embodiments of the invention, the controlled-release oral dosage form comprises opioid agonist and antagonist in the form of melt-extruded multiparticulates. The term "multiplarticulates," as used herein refers to a plurality of units, preferably within a range of similar size and/or shape and containing the opioid agonist and antagonist and a controlled-release carrier.

If the release rate of the opioid agonist and the antagonist are different from each other, melt-extruded multiparticulates containing the agonist may be prepared separately from those containing the agonist, and then combined together to form a controlled-release dosage form providing substantially similar release rate for the agonist and the antagonist.

The preparation of a suitable melt-extruded matrix according to the present invention may, for example, include the steps of blending the opioid agonist or antagonist, or both, together with at least one hydrophobic material and preferably the additional hydrophobic material to obtain a homogeneous mixture. The homogeneous mixture is then heated to a temperature sufficient to at least soften the mixture sufficiently to extrude the same. The resulting homogeneous mixture is then extruded to form strands. The extrudate is preferably cooled and cut into multiparticulates, such as pellets, by any means known in the art. The strands are cooled and cut into multiparticulates. The multiparticulates are then divided into unit doses. The extrudate preferably has a diameter of from about 0.1 to about 8 mm , more preferably about 0.1 to about 5 mm, and provides controlled release of the drug contained therein for a time period of from about 8 to about 24 hours.

An optional process for preparing the melt extrusions of the present invention includes directly metering into an extruder a hydrophobic material, a therapeutically active agent, and an optional binder; heating the homogenous mixture; extruding the homogenous mixture to thereby form strands; cooling the strands containing the homogeneous mixture; cutting the strands into particles and dividing them into unit doses. In this aspect of the invention, a relatively continuous manufacturing procedure is realized.

The diameter of the extruder aperture or exit port can also be adjusted to vary the thickness of the extruded strands. Furthermore, the exit part of the extruder need not be round; it can be oblong, rectangular, etc. The exiting strands can be reduced to particles using a hot wire cutter, guillotine, etc.

The melt-extruded multiparticulates may be compressed into tablets, as described in U.S. Patent No. 4,957,681. Alternatively, the multiparticulates may be loaded into capsules.

In certain embodiments of the invention, the opioid agonist and/or antagonist may be coated with a coating that slows down its release. The opioid agonist or antagonist may be prepared as granulates, pellets, spheroids or beads, before it is coated with the coating. The coated drug may be combined with the uncoated counterpart and compressed into a tablet core, which is then coated with a controlled-release coating. The coating for the opioid antagonist or agonist particles and the tablet core may comprise a hydrophobic material selected from an alkycellulose, an acrylic polymer or mixtures thereof, and may be applied as an organic or aqueous dispersion. The coating may be applied to obtain a weight gain from about 2 to about 25% of the substrate in order to obtain a desired sustained release profile. Coatings derived from aqueous dispersions are described, e.g., in detail in U.S. Patent Nos. 5,273,760 and 5,286,493, assigned to the Assignee of the present invention and hereby incorporated by reference.

Other examples of sustained release formulations and coatings which may be used in accordance with the present invention include Assignee's U.S. Patent Nos. 5,324,351; 5,356,467, and 5,472,712, hereby incorporated by reference in their entirety.

DETAILED DESCRIPTION OF CERTAIN PREFERRED EMBODIMENTS

The following examples illustrate various aspects of the present invention. They are not to be construed to limit the claims in any manner whatsoever.

EXAMPLE 1

In Example 1, controlled release tablets containing an opioid agonist (oxycodone HCl) and opioid antagonist (naltrexone HCl) are prepared in which both drugs are present as granulates, the granulates comprising the opioid agonist and the antagonist dispersed in a controlled release matrix. The granulates are combined with melted wax (stearyl alcohol) to produce waxed granulates, which are then milled and mixed with other excipients and compressed into tablets.

Ingredient	***Amt/unit (mg)***	***Amt/batch (kg)***
Oxycodone HCl	10.00	11.00
Naltrexone HCl	0.50	0.55
Spray Dried Lactose	68.75	75.62
Povidone	5.00	5.50
Eudragit RS 30D (dry wt.)	10.00	11.00
Triacetin	2.00	2.20
Stearyl Alcohol	25.00	27.50
Talc	2.50	2.75
Magnesium Stearate	1.25	1.38
Opadry White	5.00	5.50
Purified Water		31.16*
Total	130.00	143.00

* Remains in product as residual moisture only.

PROCESS:

1. Solution Preparation — Plasticize the Eudragit with Triacetin by mixing. Dissolve Naltrexone HCl into the plasticized solution.
2. Granulation — Place Oxycodone HCl, Spray Dried Lactose, and Povidone into a fluid bed granulator and apply the above solution.
3. Milling — Pass the granulation through a rotating impeller mill.
4. Drying — Dry granulation if moisture content is too high.
5. Waxing — Melt Stearyl Alcohol and wax the above granulation by adding melted Stearyl Alcohol onto granulation while mixing.

6. Cooling	Cool the waxed granulation in a fluid bed dryer.
7. Milling	Pass the cooled waxed granulation through a rotating impeller mill.
8. Blending	Blend the milled waxed granulation, Talc and Magnesium Stearate.
9. Compression	Compress the resultant granulation using a tablet press.
10. Coating	Prepare a film coating solution by dispersing the Opadry in Purified Water and applying it to the tablet cores.

EXAMPLE 2

In Example 2, controlled release tablets containing an opioid agonist (morphine sulfate) and opioid antagonist (naltrexone HCl) are prepared. The controlled release tablets comprise granulates comprising the opioid agonist and the antagonist dispersed in a controlled-release matrix. The granulates are combined with melted wax (cetostearyl alcohol) to produce waxed granulates, which are then milled and mixed with other excipients and compressed into tablets.

Ingredient	***Amt/unit (mg)***	***Amt/batch (kg)***
Morphine Sulfate (pentahydrate)	30.00	108.0
Naltrexone HCl	0.50	1.8
Spray Dried Lactose	69.5	250.2
Hydroxyethyl Cellulose	10.0	36.0
Purified Water		75.9*
Cetostearyl Alcohol	35.0	126.0
Talc	3.0	10.8
Magnesium Stearate	2.0	7.2
Opadry Purple	3.0	10.8
Purified Water		61.2*
Total	153.0	550.8

* Remains in product as residual moisture only.

PROCESS:

1. Solution Preparation	Dissolve Naltrexone HCl in Purified Water by mixing.
2. Granulation	Place Morphine Sulfate, Spray Dried Lactose, and Hydroxyethyl Cellulose in a mixer and granulate with Naltrexone HCl solution above.
3. Drying	Dry the above granulation in a fluid bed dryer.
4. Milling	Pass the granulation through a mill.
5. Drying	Dry granulation if moisture content is too high.
6. Waxing	Melt Cetostearyl Alcohol and wax the above granulation by adding melted Cetostearyl Alcohol onto granulation while mixing.
7. Cooling	Cool the waxed granulation in a fluid bed dryer.
8. Milling	Pass the cooled waxed granulation through a mill.
9. Blending	Blend the milled waxed granulation, Talc and Magnesium Stearate.
10. Compression	Compress the resultant granulation using a tablet press.
11. Coating	Prepare a film coating solution by dispersing the Opadry in Purified Water and applying it to the tablet cores.

EXAMPLE 3

In Example 3, controlled-release capsules containing an opioid agonist (hydromorphone HCl) and opioid antagonist (naltrexone) are prepared. Extruded drug-containing pellets are prepared by combining a wax with ethylcellulose and eudragit and feeding the mixture into a twin screw extruder. The pellets are then filled into hard gelatin capsules.

FORMULA:

Ingredient	*Amt/unit (mg)*	*Amt/batch (gm)*
Hydromorphone HCl	12.0	120.0
Eudragit RSPO	76.0	760.0
Ethylcellulose	4.5	45.0
Stearyl Alcohol	27.0	270.0
Naltrexone HCl	0.5	5.0

Hard Gelatin Capsules	√	√
Total	120.0	1200.0

PROCESS:

1.	Milling	Pass stearyl alcohol flakes through an impact mill.
2.	Blending	Mix Hydromorphone HCl, Eudragit, Ethycellulose, milled Stearyl Alcohol, and Naltrexone HCl in a twin shell blender.
3.	Extrusion	Continuously feed the blended material into a twin screw extruder and collect the resultant strands on a conveyor.
4.	Cooling	Allow the strands to cool a Conveyor.
5.	Pelletizing	Cut the cooled strands into pellets using a Pelletizer.
6.	Screening	Screen the pellets and collect desired sieve portion.
7.	Encapsulation	Fill the extruded pellets into hard gelatin capsules at 120 mg.

EXAMPLE 4

In Example 4, controlled-release tablets containing an opioid agonist (hydrocodone bitartrate) and opioid antagonist (naltrexone HCl) are prepared. The tablets contain the drugs in the form of extruded pellets.

Ingredient	*Amt/unit (mg)*	*Amt/batch (kg)*
Hydrocodone Bitartrate	30.0	15.0
Naltrexone HCl	0.5	0.25
Stearyl Alcohol	44.0	22.0
Anhydrous Dicalcium Phosphate (Powdered)	62.0	31.0
Microcrystalline Cellulose	62.0	31.0
Glyceryl Behenate	20.0	10.0
Magnesium Stearate	2.0	1.0
Opadry Red	10.0	5.0
Purified Water		28.4*
Total	230.5	115.25

* Remains in product as residual moisture only.

PROCESS:

1. Milling — Pass the Stearyl Alcohol flakes through an occillating mill.
2. Blending — Mix the Hydrocodone Bitartrate, Naloxone HCl, milled Stearyl Alcohol, Anhydrous Dicalcium Phosphate, Microcrystalline Cellulose, and Glyceryl Behenate in a twin shell blender.
3. Extrusion — Continuously feed the blended material into a twin screw extruder and collect the resultant heated material on a conveyor.
4. Cooling — Allow the extrudate to cool on the conveyor.
5. Milling — Mill the cooled extrudate using an occillating mill.
6. Blending — Blend the milled extrudate and Magnesium Stearate.
7. Compression — Compress the resultant granulation using a tablet press.

8. Coating — Prepare a film coating solution by dispersing the Opadry in Purified Water and applying it to the tablet cores.

EXAMPLE 5

In Example 5, controlled release tablets containing an opioid agonist (morphine sulfate) and opioid antagonist (naltrexone HCl) are prepared. In this Example, opioid antagonist is treated with a controlled-release carrier (Eudragit RS 30D) to modify its release rate before it is combined with the opioid agonist and formulated into a controlled-release tablet.

Ingredient	*Amt/unit (mg)*	*Amt/batch (kg)*
Naltrexone HCl	0.50	1.80
Eudragit RS 30D (dry wt.)	0.03	0.10
Triacetin	0.01	0.04
Morphine Sulfate (pentahydrate)	30.00	108.00
Spray Dried Lactose	69.46	250.06
Hydroxyethyl Cellulose	10.00	36.00
Purified Water		75.90*
Cetostearyl Alcohol	35.00	126.00
Talc	3.00	10.80
Magnesium Stearate	2.00	7.20
Opadry Purple	3.00	10.80
Purified Water		61.20*
Total	153.0	550.8

* Remains in product as residual moisture only.

PROCESS:

1. Solution Preparation — Plasticize the Eudragit by mixing with Triacetin.
2. Pre-Granulation — Pre-granulate the Naltrexone HCl in a fluid bed granulator by applying the above solution.

3. Granulation	Place Naltrexone HCl granulation (from above), Morphine Sulfate, Spray Dried Lactose, and Hydroxyethyl Cellulose in a mixer and granulate with Purified Water.
4. Drying	Dry the above granulation in a fluid bed dryer.
5. Milling	Pass the granulation through a mill.
6. Drying	Dry granulation if moisture content is too high.
7. Waxing	Melt Cetostearyl Alcohol and wax the above granulation by adding melted Cetostearyl Alcohol onto granulation while mixing.
8. Cooling	Cool the waxed granulation in a fluid bed dryer.
9. Milling	Pass the cooled waxed granulation through a mill.
10. Blending	Blend the milled waxed granulation, Talc and Magnesium Stearate.
11. Compression	Compress the resultant granulation using a tablet press.
12. Coating	Prepare a film coating solution by dispersing the Opadry in Purified Water and applying it to the tablet cores.

WHAT IS CLAIMED IS:

1. A controlled-release dosage form comprising opioid agonist and opioid antagonist, the dosage form releasing the opioid agonist and the opioid antagonist in a controlled-release manner.

2. The controlled-release dosage form of claim 1, wherein the opioid agonist and antagonist are released at a rate that allows an analgesically effective blood level of the agonist to be maintained during the dosing period.

3. The controlled-release dosage form of claim 1, wherein the opioid antagonist is released at a rate that allows the blood level of the opioid antagonist to be maintained during the dosing period that is effective in decreasing opioid related side effects but not sufficient for negating the analgesic efficacy of the agonist.

4. The controlled-release dosage form of claim 1, wherein the opioid agonist and the antagonist are released at substantially proportionate rates.

5. The controlled-release dosage form of claim 2, wherein the side effects comprise nausea, vomiting, pruritis, respiratory depression and/or urinary retention.

6. The controlled-release dosage form of claim 2, wherein the opioid antagonist is present in an amount effective in attenuating the opioid-related physical dependence.

7. The controlled-release dosage form of claim 1, wherein the dosage form comprises a transdermal delivery device, an oral mucosal delivery device, a composition for intranasal administration, an injectable composition, or a suppository.

8. The controlled-release dosage form of claim 1, wherein the dosage form comprises a solid, oral dosage form.

9. The controlled-release dosage form of claim 8, wherein the agonist and the antagonist are present as granulates, the granulates comprising the opioid agonist and the opioid antagonist dispersed in a controlled-release matrix.

10. The controlled-release dosage form of claim 7, wherein the controlled-release matrix comprises Eudragit RS 30D or ethylcellulose.

11. The controlled-release dosage form of claim 8, wherein the opioid agonist and the antagonist are present as melt-extruded pellets.

12. The controlled-release dosage form of claim 8, wherein the opioid agonist and the antagonist are present as particles coated with a coating comprising a controlled-release carrier, wherein the particles include granules, pellets and spheroids.

13. The controlled-release oral dosage form of claim 8, wherein the opioid antagonist is treated to modify its release rate before it is combined with the opioid agonist, such that when the opioid agonist and the treated antagonist are combined into the controlled-release dosage form, the opioid agonist and antagonist are released from the dosage form at substantially proportionate rates.

14. The controlled-release oral dosage form of claim 8, wherein the opioid antagonist is treated to modify its release rate before it is combined with the opioid agonist, such that when the opioid agonist and the treated antagonist are combined into the controlled-release dosage form, the dosage form releases the agonist and the antagonist at such rate that the blood levels of the agonist are maintained within the

analgesically effective range and the blood levels of the antagonist are maintained within the pharmacologically effective range for reducing the opioid agonist associated side effects over a period of time.

15. The controlled-release oral dosage form of claim 13, wherein the treated opioid antagonist comprises opioid antagonist dispersed in a controlled-release matrix, the controlled release matrix slowing the release rate of the opioid antagonist such that when it is combined with the opioid agonist in the controlled-release dosage form, the opioid antagonist and the agonist are released at substantially proportionate rates.

16. The controlled-release oral dosage form of claim 1, wherein the opioid antagonist is present as granulates comprising the opioid antagonist dispersed in a first controlled release matrix, and wherein the opioid agonist is present as granulates comprising the opioid agonist dispersed in a second controlled-release matrix, the first controlled-release matrix providing controlled-release of the opioid antagonist and the second matrix, which is different from the first matrix, providing controlled-release of the opioid agonist.

17. The controlled-release oral dosage form of claim 16, wherein the oral dosage form releases the opioid agonist and the antagonist at substantially proportionate rates.

18. The controlled-release oral dosage form of claim 16, wherein the dosage form comprises a tablet or a capsule.

19. The controlled-release oral dosage form of claim 15, wherein the opioid antagonist is prepared as granulates comprising the antagonist dispersed in a controlled-release matrix, said granulates being combined with the opioid agonist and a controlled-release carrier to prepare the controlled release dosage form.

20. The controlled-release oral dosage form of claim 13, wherein treated opioid antagonist comprises the opioid antagonist particles coated with a controlled-release coating.

21. The controlled-release oral dosage form of claim 20, wherein the controlled-release dosage form is a tablet comprising the coated opioid antagonist particles and opioid agonist interdispersed in a controlled-release matrix.

22. The controlled-release oral dosage form of claim 8, wherein the opioid antagonist is selected from the group consisting of naltrexone, naloxone, nalmephene, cyclazocine, levallorphan, and pharmaceutically acceptable salts thereof.

23. The controlled-release oral dosage form of claim 8, wherein the opioid agonist is selected from the group consisting of oxycodone, morphine, hydromorphone, hydrocodone and pharmaceutically acceptable salts thereof, and the opioid antagonist comprises naltrexone or a pharmaceutically acceptable salt thereof.

24. The controlled-release oral dosage form of claim 8, wherein the opioid agonist is selected from the group consisting of oxycodone HCl, morphine sulfate, hydromorphone HCl and hydrocodone bitartrate, and the opioid antagonist comprises naltrexone HCl.

25. The controlled-release oral dosage form of claim 8, wherein the opioid agonist is selected from the group consisting of oxycodone, morphine, hydromorphone, hydrocodone and pharmaceutically acceptable salts thereof, and the opioid antagonist comprises naloxone or a pharmaceutically acceptable salt thereof

26. The controlled-release oral dosage form of claim 8, wherein the opioid agonist is selected from the group consisting of oxycodone HCl, morphine sulfate, hydromorphone HCl and hydrocodone bitartrate, and the opioid antagonist comprises naltrexone HCl.

27. The controlled-release dosage form of claim 8 wherein the ratio of the opioid agonist to opioid antagonist is about 1:1 to about 1:100 by weight.

28. The controlled-release dosage form of claim 8 wherein the weight ratio of the opioid agonist to opioid antagonist is about 1:20 to about 1:100 by weight.

29. The controlled-release dosage form of claim 8 wherein the weight ratio of the opioid agonist to opioid antagonist is about 1:20 to about 1:40.

30. The controlled-release dosage form of claim 1, wherein the dosage form provides controlled-release of the opioid agonist and opioid antagonist over about 8 hour period.

31. The controlled-release dosage form of claim 1, wherein the dosage form provides controlled-release of the opioid agonist and opioid antagonist over about 12 hour period.

32. The controlled-release dosage form of claim 1, wherein the dosage form provides controlled-release of the opioid agonist and opioid antagonist over about 24 hour period.

33. A method of preparing a dosage composition comprising an opioid agonist and an opioid antagonist, the method comprising: (i) pretreating either the opioid agonist or

the opioid antagonist to modify its release rate; and (ii) combining the pretreated drug with the other drug to produce the dosage form.

34. The method of claim 33, wherein the drug that is combined with the pretreated drug is also pretreated to modify its release rate before the combination.

35. The method of claim 33, wherein the dosage form comprises a controlled-release dosage form that provides controlled-release of both the opioid agonist and the opioid antagonist.

36. The method of claim 34, wherein the dosage form comprises a controlled-release dosage form that provides controlled-release of both the opioid agonist and the opioid antagonist.

ABSTRACT

Controlled-release dosage forms comprising opioid agonist and opioid antagonist are provided. The dosage forms release the opioid antagonist and the opioid agonist in a controlled-release manner. The dosage forms may be used to provide pain relief to patients while reducing the side effects associated with opioid agonists.

II. PENDING CLAIMS

Claims 1-36 (Cancelled)

Claim 37. A transdermal delivery system for an opioid analgesic, comprising an opioid agonist and an opioid antagonist contained in a reservoir or matrix and capable of delivery from the system in a controlled manner, such that when the system is applied to the skin of a human patient, the opioid agonist and the opioid antagonist are release at substantially proportionate rates, the opioid agonist is delivered at a mean relative release rate effective to provide analgesia to the patient for at least 3 days, and the opioid antagonist is delivered at a mean relative release rate sufficient to reduce a side effect associated with the opioid agonist, said antagonist selected from the group consisting of naloxene, naltrexone, cylazocine, levallorphan and pharmaceutically acceptable salts thereof.

Claims 38-39 (Cancelled)

Claim 40. The transdermal delivery system of claim 37, wherein said opioid antagonist comprises naloxene or a pharmaceutically acceptable salt thereof.

Claim 41. The transdermal delivery system of claim 37, wherein said opioid antagonist comprises naltrexone or a pharmaceutically acceptable salt thereof.

Claim 42. The transdermal delivery system of claim 37, wherein said opioid agonist is selected from the group consisting of alfentanil, allylprodine, alphaprodine, anileridine, benzylmorphine, bezitramide, buprenorphine, butorphanol, clonitazene, codeine, desomorphine, dextromoramide, dezocine, diampromide, diamorphone, dihydrocodeine, dihydromorphine, dimenoxadol, dimenpheptanol, dimethylthiambutene, dioxaphetyl butyrate, dipipanone, eptazoine, ethoheptazine, ethylmethylthiambutene, ethylmorphine, etonitazene, fentanyl, heroin, hydrocodone, hydromorphone, hydroxypethidine, isomethadone, ketobedmidone, levorphanol, levophenacylmorphan, lofentanil,

meperidine, meptazinol, metazocine, methadone, metopon, morphine, myrophine, narceine, nicomorphine, norlevorphanol, normethadone, nalorphine, nalbuphene, normorphine, norpipanone, opium, oxycodone, oxymorphone, papavertum, pentazocine, phenadoxone, phenomorphan, phenazocine, phenoperidine, piminodine, piritramide, propheptazine, promedol, properidine, propoxyphene, sufentanil, tilidine, tramadol, mixtures thereof and pharmaceutically acceptable salts thereof.

Claim 43. The transdermal delivery system of claim 42, wherein said opioid agonist comprises fentanyl or a pharmaceutically acceptable salt thereof.

Claim 44. The transdermal delivery system of claim 42, wherein said opioid agonist comprises buprenorphine or a pharmaceutically acceptable salt thereof.

Claim 45. The transdermal delivery system of claim 42, wherein said opioid agonist comprises morphine or a pharmaceutically acceptable salt thereof.

Claim 46. The transdermal delivery system of claim 42, wherein said opioid agonist comprises hydromophone or a pharmaceutically acceptable salt thereof.

Claim 47. The transdermal delivery system of claim 42, wherein said opioid agonist comprises oxycodone or a pharmaceutically acceptable salt thereof.

Claim 48. (Cancelled)

Claim 49. The transdermal delivery system of claim 37, wherein the opioid antagonist is treated to modify its release rate before it is combined with the opioid agonist, such that when the opioid agonist and the treated antagonist are combined into the transdermal delivery system, the opioid agonist and antagonist are released from the system at substantially proportionate rates.